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Application of
HABERMANN, et al.

Examiner:

Group Art Unit.: 1614

Application No.: 10/065,994 ✓

Filed: December 9, 2002 ✓

Title: **PYRIDINE-2,4-DICARBOXYLIC
ACID DIAMIDES AND PYRIMIDINE-
4,6-DICARBOXYLIC ACID DIAMIDES
AND THE USE THEREOF FOR
SELECTIVELY INHIBITING
COLLAGENASES** ✓

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**SUBMISSION AND REQUEST FOR ENTRY OF VERIFIED TRANSLATION
OF NON-ENGLISH LANGUAGE PAPERS**

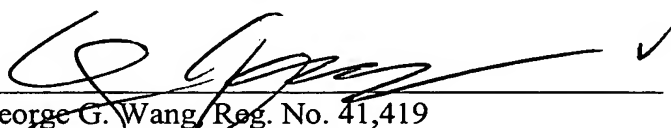
Dear Sir:

Applicants submit herewith an English translation of U.S. Provisional Application No. 60/358,887 filed 02/22/02. Also submitted herewith is a statement by the translator of the accuracy of the translation. Applicants previously claimed priority of said U.S. provisional application under U.S.C. § 119.

This submission and request for entry is being made to satisfy the requirements under 37 C.F.R. 1.78(a)(5).

The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment, to Account No. 18-1982. Two duplicate copies of this sheet are enclosed.

Respectfully submitted,


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Aventis Docket No. DEAV2001/0073 US PSP



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I, Susan ANTHONY BA, ACIS,

Director of RWS Group plc, of Europa House, Marsham Way, Gerrards Cross,
Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.
2. That the translator responsible for the attached translation is well acquainted with the German and English languages.
3. That the attached is, to the best of RWS Group plc knowledge and belief, a true translation into the English language of the specification in German filed with the application for a patent in the U.S.A. on 22 February 2002
under the number 60/358,887
4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Group plc

The 21st day of March 2003

Use of pyridine-2,4-dicarboxylic acid diamides and pyrimidine-4,6-dicarboxylic acid diamides for selectively inhibiting collagenases

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The invention relates to the use of pyridine-2,4-dicarboxylic acid diamides and pyrimidine-4,6-dicarboxylic acid diamides for selectively inhibiting collagenase (MMP 13). The pyridine-2,4-dicarboxylic acid diamides and pyrimidine-4,6-dicarboxylic acid diamides can therefore be employed for treating degenerative diseases of the joints.

10

It is known that pyrimidine-4,6-dicarboxylic acid diamides and 2,4-substituted pyridine-N-oxides inhibit the enzymes proline hydroxylase and lysine hydroxylase and thereby bring about an inhibition of collagen biosynthesis by influencing the collagen-specific hydroxylation reaction (EP 0418797; EP 0463592). This inhibition of collagen biosynthesis results in the formation of a nonfunctional, underhydroxylated collagen molecule which can only be released by the cells into the extracellular space in small quantity. In addition, the underhydroxylated collagen cannot be incorporated into the collagen matrix and is very easily broken down proteolytically. As a consequence of these effects, the overall quantity of extracellularly deposited collagen decreases.

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In diseases such as osteoarthritis and rheumatism, the joint is destroyed, due, in particular, to the proteolytic degradation of collagen by collagenases. Collagenases belong to the metalloproteinase (MP) or matrix metalloproteinase (MMP)

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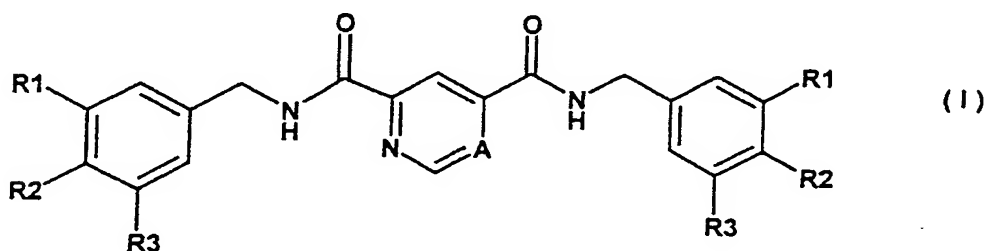
superfamily. MMPs cleave collagen, laminin, proteoglycans, elastin or gelatin under physiological conditions and therefore play an important role in bone and connective tissue. A large number of different inhibitors of the MMPs or the collagenases are known (EP 0 606 046; WO94/28889). The known inhibitors of the MMPs frequently suffer from the disadvantage that they lack the specificity of inhibiting only one class of the MMPs. As a result, most MMP inhibitors inhibit several MMPs at the same time because the catalytic domains of the MMPs exhibit similar structures. As a consequence, the inhibitors act, in an undesirable manner, on many enzymes, including those which have a vital function (Massova I., et al., The FASEB Journal (1998) 12, 1075-1095).

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In an endeavor to find active compounds for treating connective tissue diseases, it has now been found that the compounds which are employed in accordance with the invention are powerful inhibitors of matrix metalloproteinase 13 whereas they are essentially inactive in the case of MMPs 3 and 8.

5

The invention therefore relates to the use of compounds of the formula I



and/or all stereoisomeric forms of the compound of the formula I and/or mixtures of these forms in any ratio, and/or a physiologically tolerated salt of the compound of formula I, for producing a pharmaceutical for the prophylaxis and therapy of diseases whose course involves an increased activity of matrix metalloproteinase 13, where

10

A is a carbon atom or nitrogen atom,

15 R1 and R3 are identical or different and, independently of each other, are

1. hydrogen atom,
2. halogen,
3. $-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
4. $-O-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
5. $-C(O)-O-R_4$, in which R_4 is hydrogen atom or $-(C_1-C_4)$ -alkyl,
6. $-CN$,
7. $-N(R_5)(R_6)$, in which R_5 and R_6 are identical or different and are, independently of each other,

20

25

1. hydrogen atom,
2. $-(C_1-C_4)$ -alkyl,
3. $-C(O)-(C_1-C_4)$ -alkyl or
4. $-SO_2-(C_1-C_4)$ -alkyl,

8. -OH,
9. -S-(C₁-C₄)-alkyl,
10. -S(O)-(C₁-C₄)-alkyl,
11. -S(O)₂-R₇, in which R₇ is -(C₁-C₄)-alkyl, -OH or -NH₂,

5

- R₂ is
1. hydrogen atom,
 2. halogen,
 3. -O-(C₁-C₄)-alkyl,
 4. -(C₁-C₄)-alkyl,
 - 10 5. -C(O)-O-R₄, in which R₄ is hydrogen atom or -(C₁-C₄)-alkyl,
 6. -CN,
 7. -N(R₅)(R₆), in which R₅ and R₆ are identical or different and are,
independently of each other,
 1. hydrogen atom,
 - 15 2. -(C₁-C₄)-alkyl,
 3. -C(O)-(C₁-C₄)-alkyl or
 4. -SO₂-(C₁-C₄)-alkyl,
 8. -OH,
 9. -S-(C₁-C₄)-alkyl,
 - 20 10. -S(O)-(C₁-C₄)-alkyl,
 11. -S(O)₂-R₇, in which R₇ is -(C₁-C₄)-alkyl, -OH or -NH₂, or

25 R₁ and R₂ or R₂ and R₃ form, together with the carbon atoms to which they are in each case bonded, a 5- or 6-membered ring which is aromatic or saturated and contains zero, one or two heteroatoms from the series oxygen, nitrogen or sulfur, and

the other radical R₁ or R₃ has the abovementioned meaning of 1. to 11.

The invention furthermore relates to the use of compounds of the formula I where

30 A is a carbon atom or nitrogen atom,

R₁ and R₃ are identical or different and are, independently of each other,

1. hydrogen atom,

2. halogen,
3. $-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
4. $-O-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,

- R2 is
1. hydrogen atom,
 2. halogen,
 3. $-O-(C_1-C_4)$ -alkyl, or
 4. $-(C_1-C_4)$ -alkyl, or

R1 and R2 or R2 and R3 form, together with the carbon atoms to which they are in each case bonded, a 5- or 6-membered ring which is aromatic or saturated and contains zero, one or two heteroatoms from the series oxygen, nitrogen or sulfur, and

the other radical R1 or R3 has the abovementioned meaning of 1. to 4.

The invention furthermore relates to the use of compounds of the formula I where

A is a carbon atom or nitrogen atom,

R1 and R3 are identical or different and are, independently of each other,

1. hydrogen atom,
2. chlorine,
3. fluorine,
4. trifluoromethyl,
5. methoxyl,
6. methyl,
7. $-C(O)-OH$,
8. $-C(O)-O-CH_3$,
9. $-CN$,
10. $-NH_2$,
11. $-NH-C(O)-CH_3$,
12. $-NH-SO_2-CH_3$,

- | | | | |
|----|-------|-----|------------------------------------------|
| | | 13. | -N-(CH ₃) ₂ , |
| | | 14. | -SO ₂ -NH ₂ , |
| | | 15. | -OH, |
| | | 16. | -O-CH ₂ -(CHF ₂), |
| 5 | | 17. | -S-CH ₃ , |
| | | 18. | -S(O)-CH ₃ , |
| | | 19. | -S(O) ₂ -CH ₃ or |
| | | 20. | bromine, |
| 10 | R2 is | 1. | hydrogen atom, |
| | | 2. | chlorine, |
| | | 3. | fluorine, |
| | | 4. | methoxyl, |
| | | 5. | methyl, |
| 15 | | 6. | bromine, |
| | | 7. | -C(O)-OH, |
| | | 8. | -C(O)-O-CH ₃ , |
| | | 9. | -CN, |
| | | 10. | -NH ₂ , |
| 20 | | 11. | -NH-C(O)-CH ₃ , |
| | | 12. | -NH-SO ₂ -CH ₃ , |
| | | 13. | -N-(CH ₃) ₂ , |
| | | 14. | -SO ₂ -NH ₂ , |
| | | 15. | -OH, |
| 25 | | 16. | -O-CH ₂ -(CHF ₂), |
| | | 17. | -S-CH ₃ , |
| | | 18. | -S(O)-CH ₃ or |
| | | 19. | -S(O) ₂ -CH ₃ , or |

30 R1 and R2 or R2 and R3 form, together with the carbon atoms to which they are in each case bonded, a dioxolane, dihydrofuran or furan ring, and the other radical R1 or R3 has the abovementioned meaning of 1. to 20.

The invention furthermore relates to the use of compounds of the formula I where
A is a carbon atom or nitrogen atom,

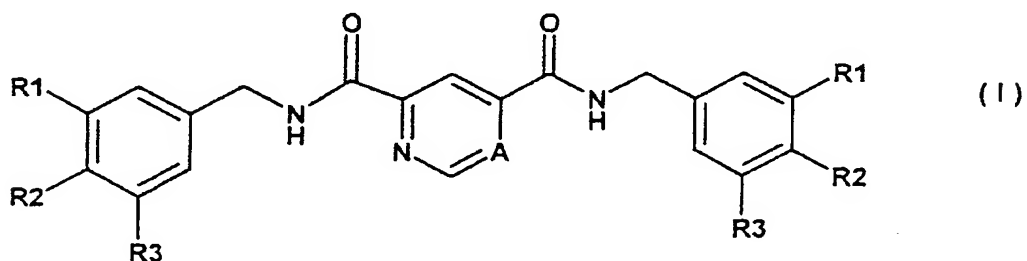
R1 and R3 are identical or different and are, independently of each other,

- 5 1. hydrogen atom,
 2. chlorine,
 3. fluorine,
 4. trifluoromethyl,
 5. methoxyl, or
10 6. methyl,

- R2 is 1. hydrogen atom,
 2. chlorine,
 3. fluorine,
15 4. methoxyl, or
 5. methyl, or

R1 and R2 or R2 and R3 form, together with the carbon atoms to which they are in
each case bonded, a dioxolane, dihydrofuran or furan ring.

20 The invention furthermore relates to the compounds of the formula I,



and/or all the stereoisomeric forms of the compound of the formula I, and/or mixtures
of these forms in any ratio, and/or a physiologically tolerated salt of the compound of
the formula I, where

25 A is a carbon atom or nitrogen atom,

R1 and R3 are identical or different and, independently of each other, are

1. hydrogen atom,
2. -(C₁-C₄)-alkyl, in which alkyl is substituted once, twice or three times
by halogen,

3. -O-(C₁-C₄)-alkyl, in which alkyl is substituted once, twice or three times by halogen,
4. -OH,
5. -C(O)-O-R₄, in which R₄ is hydrogen atom or -(C₁-C₄)-alkyl,
- 5 6. -CN,
7. -N(R₅)-R₆, in which R₅ and R₆ are identical or different and are, independently of each other,
 1. hydrogen atom,
 2. -(C₁-C₄)-alkyl,
 - 10 3. -C(O)-(C₁-C₄)-alkyl or
 4. -SO₂-(C₁-C₄)-alkyl,
 8. -S-(C₁-C₄)-alkyl,
 9. -S(O)-(C₁-C₄)-alkyl, or
 10. -S(O)₂-R₇, in which R₇ is -(C₁-C₄)-alkyl, -OH or -NH₂,
- 15 in which R₁, R₂ and R₃ are not simultaneously hydrogen atom, and R₂ is
 1. hydrogen atom,
 2. halogen,
 3. -O-(C₁-C₄)-alkyl,
 4. -(C₁-C₄)-alkyl,
 - 20 5. -C(O)-O-R₄, in which R₄ is hydrogen atom or -(C₁-C₄)-alkyl,
 6. -CN,
 7. -N(R₅)(R₆), in which R₅ and R₆ are identical or different and are, independently of each other,
 1. hydrogen atom,
 - 25 2. -(C₁-C₄)-alkyl,
 3. -C(O)-(C₁-C₄)-alkyl, or
 4. -SO₂-(C₁-C₄)-alkyl,
 8. -OH,
 9. -S-(C₁-C₄)-alkyl,
 - 30 10. -S(O)-(C₁-C₄)-alkyl, or
 11. -S(O)₂-R₇, in which R₇ is -(C₁-C₄)-alkyl, -OH or -NH₂, or

R1 and R2 or R2 and R3 form, together with the carbon atoms to which they are in each case bonded, a 5- or 6-membered ring which is aromatic or saturated and contains zero, one or two heteroatoms from the series oxygen, nitrogen or sulfur, and

5 the other radical R1 or R3 is

1. hydrogen atom,
2. halogen,
3. $-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
- 10 4. $-O-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
5. $-C(O)-O-R_4$, in which R4 is hydrogen atom or $-(C_1-C_4)$ -alkyl,
6. $-CN$,
- 15 7. $-N(R_5)-(R_6)$, in which R5 and R6 are identical or different and are, independently of each other,

1. hydrogen atom,
2. $-(C_1-C_4)$ -alkyl,
3. $-C(O)-(C_1-C_4)$ -alkyl or
4. $-SO_2-(C_1-C_4)$ -alkyl or

- 20 8. $-OH$,
9. $-S-(C_1-C_4)$ -alkyl,
10. $-S(O)-(C_1-C_4)$ -alkyl or
11. $-S(O)_2-R_7$, in which R7 is $-(C_1-C_4)$ -alkyl, $-OH$ or $-NH_2$.

25 The invention furthermore relates to a compound of the formula I, where
A is a carbon atom or nitrogen atom,

R1 and R3 are identical or different and are, independently of each other,

1. hydrogen atom,
- 30 2. chlorine,
3. fluorine,
4. trifluoromethyl,
5. methoxyl,

- | | | |
|----|-----|------------------------------------------|
| | 6. | methyl, |
| | 7. | -C(O)-OH, |
| | 8. | -C(O)-O-CH ₃ , |
| | 9. | -CN, |
| 5 | 10. | -NH ₂ , |
| | 11. | -NH-C(O)-CH ₃ , |
| | 12. | -NH-SO ₂ -CH ₃ , |
| | 13. | -N-(CH ₃) ₂ , |
| | 14. | -SO ₂ -NH ₂ , |
| 10 | 15. | -OH, |
| | 16. | -O-CH ₂ -(CHF ₂), |
| | 17. | -S-CH ₃ , |
| | 18. | -S(O)-CH ₃ , |
| | 19. | -S(O) ₂ -CH ₃ or |
| 15 | 20. | bromine, |

in which R1, R2 and R3 are not simultaneously hydrogen atom, and

R2 is

- | | | |
|----|-----|------------------------------------------|
| | 1. | hydrogen atom, |
| | 2. | chlorine, |
| | 3. | fluorine, |
| 20 | 4. | methoxyl, |
| | 5. | methyl, |
| | 6. | bromine, |
| | 7. | -C(O)-OH, |
| | 8. | -C(O)-O-CH ₃ , |
| 25 | 9. | -CN, |
| | 10. | -NH ₂ , |
| | 11. | -NH-C(O)-CH ₃ , |
| | 12. | -NH-SO ₂ -CH ₃ , |
| | 13. | -N-(CH ₃) ₂ , |
| 30 | 14. | -SO ₂ -NH ₂ , |
| | 15. | -OH, |
| | 16. | -O-CH ₂ -(CHF ₂), |

17. -S-CH₃,
18. -S(O)-CH₃ or
19. -S(O)₂-CH₃, or

5 R1 and R2 or R2 and R3 form, together with the carbon atoms to which they are in each case bonded, a dioxolane, dihydrofuran or furan ring, and the other radical R1 or R3 has the abovementioned meaning of 1. to 20.

10 The invention furthermore relates to the compounds of the formula I, and/or all the stereoisomeric forms of the compound of the formula I, and/or mixtures of these forms in any ratio, and/or a physiologically tolerated salt of the compound of the formula I, where

A is a carbon atom or nitrogen atom,

- 15 R1 and R3 are identical or different and are, independently of each other,
1. hydrogen atom,
 2. -(C₁-C₄)-alkyl, in which alkyl is substituted once, twice or three times by halogen, or
 3. -O-(C₁-C₄)-alkyl, in which alkyl is substituted once, twice or three times by halogen,
- 20

in which R1, R2 and R3 are not simultaneously hydrogen atom, and

- R2 is
1. hydrogen atom,
 2. halogen,
 3. -O-(C₁-C₄)-alkyl, or
 - 25 4. -(C₁-C₄)-alkyl, or

R1 and R2 or R2 and R3 form, together with the carbon atoms to which they are in each case bonded, a 5- or 6-membered ring which is aromatic or saturated and contains zero, one or two heteroatoms from the series oxygen, nitrogen or sulfur, and

- 30 the other radical R1 or R3 is
1. hydrogen atom,
 2. halogen,

3. $-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen, or
4. $-O-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,

5

The invention furthermore relates to compounds of the formula I where

A is a carbon atom or nitrogen atom,

10 R1 and R3 are identical or different and are, independently of each other,

1. hydrogen atom, or
2. trifluoromethyl,

in which R1, R2 and R3 are not simultaneously hydrogen atom, and

R2 is 1. hydrogen atom,

- 15
2. chlorine,
 3. fluorine,
 4. methoxyl or
 5. methyl, or

R1 and R2 or R2 and R3 form, together with the nitrogen atoms to which they are in

20 each case bonded, a dioxolane, dihydrofuran or furan ring and

the other radical R1 or R3 is

- 25
1. hydrogen atom,
 2. chlorine,
 3. fluorine,
 4. trifluoromethyl,
 5. methoxyl, or
 4. methyl.

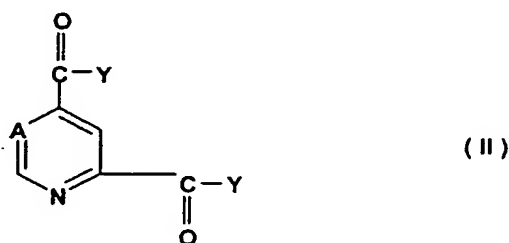
The term "halogen" is understood as meaning fluorine, chlorine, bromine or iodine.

30 The term " (C_1-C_4) -alkyl" is understood as meaning hydrocarbon radicals whose carbon chain is straight-chain or branched and contains 1 to 4 carbonatoms, for example, methyl, ethyl, propyl, i-propyl, butyl or tertiary butyl.

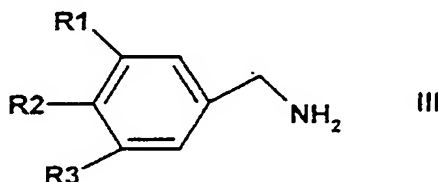
The term "R1 and R2 or R2 and R3 form, together with the carbon atoms to which the are in each case bonded, a 5- or 6-membered ring which is aromatic or saturated

and contains zero, one or two heteroatoms from the series oxygen, nitrogen or sulfur" is understood as meaning radicals which can be derived from dioxolane, pyrrole, pyrrolidine, pyridine, piperidine, tetrahydropyridine, pyrazole, imidazole, pyrazoline, imidazoline, pyrazolidine, imidazolidine, pyridazine, pyrimidine, pyrazine, 5 piperazine, pyran, furan, dihydrofuran, tetrahydrofuran, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxathiolane, thiopyran, thiazole, isothiazole, 2-isothiazoline, isothiazolidine or thiomorpholine.

The compounds of the formula I can be prepared, for example, by reacting a 10 compound of the formula II

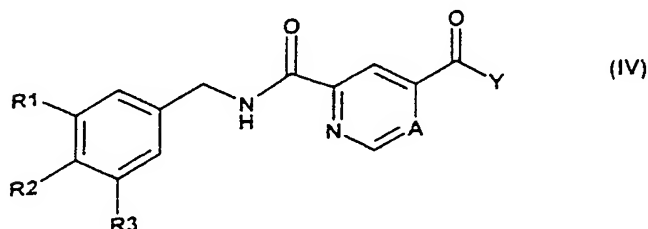


a) with a compound of the formula III



15 where R1, R2 and R3 have the meanings given in formula I and Y is halogen, hydroxy or C₁-C₄-alkoxy or, together with the carbonyl group, forms an active ester or a mixed anhydride, with a compound of the formula I being formed and the reaction products being converted, where appropriate, into their physiologically tolerated salts, or

20 b) reacting a compound of the formula II with a compound of the formula III to give a compound of the formula IV



where R1, R2 and R3 have the meanings given in formula I and Y is halogen, hydroxy or C₁-C₄-alkoxy or, together with the carbonyl group, forms an active ester or a mixed anhydride, and purifying the compound of the formula IV, where appropriate, and then converting it, with a compound of the formula III, into a compound of the formula I.

In that which follows, the preparation of compounds according to formula I and the preparation of the starting substances which are required for this purpose, insofar as they are not commercially available, are described in more detail.

The compounds according to the invention are prepared in the simplest manner by mixing together the two components, i.e. the pyrimidine or pyridine derivative according to formula (II) and the amine according to formula (III) in equimolar quantities or in up to about a 5-fold excess of III and reacting them at temperatures of between -30°C to 150°C, preferably at from 20°C up to 100°C, until the reaction has come to an end. When the compound of the formula IV is being prepared, the amine according to (III) is admixed up to an equimolar quantity of the compound of the formula III and reacted as above. The completion of the reaction can be determined, for example, with the aid of thin layer chromatography or HPLC-MS. A variant of this process is that the reaction is carried out in a suitable solvent, such as diethyl ether, dimethoxyethane or tetrahydrofuran, chlorinated hydrocarbons such as methylene chloride, chloroform or tri- or tetrachloroethylene, benzene or toluene, or else polar solvents such as dimethylformamide, acetone or dimethyl sulfoxide. In this case, too, it is possible to use an excess of amine according to formula (III), which excess can amount to up to about 5-fold quantities. The reaction temperatures in this case are between room temperature and the boiling point of the solvent, with temperatures in the range from room temperature up to 130°C being particularly preferred.

The reaction can also take place by way of a mixed anhydride such as ethyl chloroformate or by way of an active ester such as paranitrophenyl ester (Y = ClCH₂-COO or NO₂-C₆H₄-O). Corresponding methods are described in the literature.

Where appropriate, the reaction can also take place in the presence of bases. Examples of suitable additional bases are carbonates or hydrogen carbonates such as sodium carbonate or potassium carbonate or sodium hydrogen carbonate or potassium hydrogen carbonate, or tertiary amines, such as triethylamine, tributylamine or ethyldiisopropylamine, or heterocyclic amines, such as N-alkyl-morpholine, pyridine, quinoline or dialkylanilines.

Where appropriate, the products, in particular the compound of the formula IV, can be worked up, for example, by extraction or chromatography, for example through silica gel. The isolated product can be recrystallized and, where appropriate, converted into a physiologically tolerated salt using a suitable acid. Examples of suitable acids which come into consideration are:

mineral acids, such as hydrochloric acid and hydrobromic acid and also sulfuric acid, phosphoric acid, nitric acid or perchloric acid, or organic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, maleic acid, fumaric acid, phenylacetic acid, benzoic acid, methanesulfonic acid, toluenesulfonic acid, oxalic acid, 4-aminobenzoic acid, naphthalene-1,5-disulfonic acid or ascorbic acid.

Insofar as they are not commercially available, the starting compounds of the formula (III) can be readily synthesized (e.g. Organikum, Organisch Chemisches Grundpraktikum [Organikum, Basic Practical Course in Organic Chemistry], 15th edtn., VEB Deutscher Verlag der Wissenschaften [VEB German Publishing Company for the Sciences], 1976; an overview of the various options can be found in the methods index, p. 822).

The starting compounds of the formula (II) can be obtained, for example, by converting pyrimidine-4,6-dicarboxylic acid or pyridine-2,4-dicarboxylic acid, respectively, into the corresponding pyrimidine-4,6-dicarbonyl halide, or, respectively, pyridine-2,4-dicarbonyl halide, preferably chloride (using methods known from the literature), preferably in the presence of a catalyst such as dimethylformamide. This acid halide can then be reacted, for example, either with a suitable alcohol, e.g. paranitrobenzyl alcohol, to give the corresponding active ester or else with lower alcohols, such as methanol or ethanol, to give the corresponding

esters. The pyrimidine-4,6-dicarboxylic acid can also initially be converted, in the added presence of a suitable carboxylic acid or of a carboxylic ester, such as ethyl chloroformate, into a mixed anhydride, which is then reacted with the amines of the compound of the formulae (III) and (IV) to give the products according to the

5 invention. An appropriate method is also described in the literature.

The pyrimidine-4,6-dicarboxylic acid is prepared using methods known from the literature, for example by oxidizing 4,6-dimethylpyrimidine, which, for its part, can be obtained, for example, by catalytically hydrogenating commercially obtainable

10 2-mercapto-4,6-dimethylpyrimidine.

Insofar as compounds of the formula I permit diastereoisomeric or enantiomeric forms, and accrue as their mixtures in connection with the chosen synthesis, the separation into the pure stereoisomers is achieved either by chromatography on an optionally chiral support material or, insofar as the racemic compound of the formula I is capable of sulfonation, by fractional crystallization of the diastereomeric salts which are formed using an optically active base or acid as auxiliary substance. Examples of suitable chiral stationary phases for the thin-layer-chromatographic or column-chromatographic separation of enantiomers are modified silica gel supports (what are termed Pirkle phases) and also high molecular weight carbohydrates such as triacetylcellulose. Gas-chromatographic methods on chiral stationary phases can also be used for analytical purposes following appropriate derivatization, as known to the skilled person. In order to separate the racemic carboxylic acids into their enantiomers, the differently soluble diastereomeric salts are formed using an optically active base which can as a rule be obtained commercially, such as (-)-nicotine, (+)- and (-)-phenylethylamine, quinine bases, L-lysine or L- and D-arginine, the more difficultly soluble component is then isolated as a solid, the more readily soluble diastereomer is separated off from the mother liquor, and the pure enantiomers are then isolated from the diastereomeric salts which had been obtained in this way. The racemic compounds of the formula I which contain a basic group such as an amino group can in principle be converted into the pure enantiomers in the same way using optically active acids, such as (+)-camphor-10-sulfonic acid, D- and L-tartaric acid, D- and L-lactic acid and also (+) and (-)-mandelic acid. Chiral compounds which contain alcohol or amine functions can also

be converted into the corresponding esters or amides using appropriately activated or optionally N-protected enantiomerically pure amino acids or, conversely, chiral carboxylic acids can be converted into the amides using carboxy-protected enantiomerically pure amino acids or into the corresponding chiral esters using

5 enantiomerically pure hydroxycarboxylic acids such as lactic acid. The chirality of the amino acid radical or alcohol radical which has been introduced in enantiomerically pure form can then be used for separating the isomers by means of separating the diastereomers, which are now present, by crystallization or chromatography on suitable stationary phases and, after that, once again eliminating the entrained chiral
10 molecular moiety using suitable methods.

Acidic or basic products of the compound of the formula I can be present in the form of their salts or in free form. Preference is given to pharmacologically tolerated salts, for example alkali metal salts or alkaline earth metal salts or hydrochlorides,
15 hydrobromides, sulfates, hemisulfates, all the possible phosphates, and also salts of the amino acids, natural bases or carboxylic acids.

Physiologically tolerated salts are prepared in a manner known per se from compounds of the formula I, including their stereoisomeric forms, which are capable
20 of salt formation. The carboxylic acids and hydroxamic acids form stable alkali metal salts, alkaline earth metal salts or, where appropriate, substituted ammonium salts with basic reagents such as hydroxides, carbonates, hydrogen carbonates, alcoholates and ammonia or organic bases, for example trimethylamine or triethylamine, ethanolamine or triethanolamine, or else basic amino acids, for
25 example lysine, ornithine or arginine. Insofar as the compounds of the formula I possess basic groups, stable acid addition salts can also be prepared using strong acids. Both inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, 4-bromobenzenesulfonic acid, cyclohexylamidosulfonic acid,
30 trifluoromethylsulfonic acid, acetic acid, oxalic acid, tartaric acid, succinic acid or trifluoroacetic acid, are suitable for this purpose.

Because of their pharmacological properties, the compounds of the formula I are suitable for the prophylaxis and therapy of all those diseases whose course involves an increased activity of matrix metalloproteinase 13.

- 5 These diseases include degenerative joint diseases such as osteoarthroses, spondyloses, chondrolysis following joint trauma or a relatively long period of joint immobilization following injuries to the meniscus or patella or the tearing of a ligament. In addition, they also include diseases of the connective tissue such as collagenoses, periodontal diseases, wound healing disturbances and chronic
- 10 diseases of the locomotor system, such as inflammatory, immunologically or metabolism-determined acute and chronic arthritides, arthropathies, myalgias and disturbances of bone metabolism.

- The pharmaceuticals according to the invention can be administered by
- 15 subcutaneous, intraarticular, intraperitoneal or intravenous injection. Intraarticular injection is preferred. It is also possible to administer them rectally, orally, by inhalation or transdermally.

- The invention also relates to a process for producing a pharmaceutical, in which
- 20 process at least one compound of the formula I is brought, together with a pharmaceutically suitable and physiologically tolerated excipient and, where appropriate, further suitable active compounds, additives or auxiliary substances, into a suitable form for administration.

- 25 The compounds of the formula I are mixed with the additives which are suitable for this purpose, such as carrier substances, stabilizers or inert diluents and brought, using the customary methods, into suitable administration forms, such as tablets, sugar-coated tablets, hard gelatin capsules, aqueous alcoholic or oily suspensions or aqueous or oily solutions. Examples of inert carrier substances which can be used
- 30 are gum arabic, magnesium oxide, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular corn starch. In this connection, the preparation can also be effected as dry granules or wet granules. Examples of suitable oily carrier substances or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil.

For the purpose of subcutaneous, intraarticular, intraperitoneal or intravenous administration, the active compounds are, if desired, brought into solution, suspension or emulsion using the substances which are suitable for this purpose, such as solubilizers, emulsifiers or other auxiliary substances. Examples of suitable solvents are physiological sodium chloride solution or alcohols, for example ethanol, propanol or glycerol, and, in addition, sugar solutions, such as glucose or mannitol solutions, or else a mixture of the different solvents which have been mentioned.

In addition, use is made of customary adjuvants, such as carrier substances, disintegrants, binders, coating agents, swelling agents, glidants, lubricants, flavorants, sweeteners and solubilizers. Frequently employed auxiliary substances which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, cellulose and its derivatives, animal and vegetable oils, such as cod liver oil, sunflower oil, peanut oil or sesame oil, polyethylene glycol and solvents such as sterile water and monohydric or polyhydric alcohols, such as glycerol.

The compounds of formula I are preferably produced and administered as pharmaceutical preparations in dosage units, with each unit containing, as the active constituent, a particular dose of the compound of the formula I. For this purpose, they can be administered orally in doses of from 0.01 mg/kg/day to 25.0 mg/kg/day, preferably of from 0.01 mg/kg/day to 5.0 mg/kg/day, or parenterally in doses of from 0.001 mg/kg/day to 5 mg/kg/day, preferably of from 0.001 mg/kg/day to 2.5 mg/kg/day. The dose can also be increased in severe cases. However, relatively small doses suffice in many cases. These figures relate to an adult patient weighing approximately 75 kg.

The invention is explained below with the aid of examples.

Example 1:

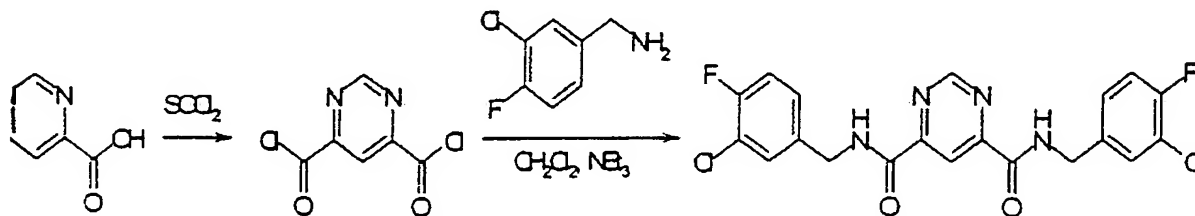
5 Pyrimidine-4,6-dicarboxylic acid dibenzylamide (formula I: R1 = R2 = H)
 1.7 g of pyrimidine-4,6-dicarboxylic acid are suspended in 20 ml of toluene and 2.4 g
 of thionyl chloride and 0.2 ml of dimethylformamide are added. The mixture is heated
 to reflux until it is no longer possible to observe any gas evolution (about 3 hours
 (h)). About 5 ml of solvent are distilled off and the mixture is then cooled down to
 10 from 0°C to 10°C and 2.7 g of benzylamine, dissolved in 10 ml of toluene, are added.
 The solution is slowly heated to room temperature, then stirred at room temperature
 for 12 hours and evaporated down to dryness. The residue is taken up in 50 ml of
 methylene chloride and the solution is extracted 3 times by shaking with saturated
 sodium hydrogen carbonate solution; the organic phase is washed with water, dried
 15 with magnesium sulfate and evaporated.

The solid is recrystallized from diisopropyl ether. Yield: 2.1 g; m.p.: 131°C to 132°C.

Example 2:

20

Pyrimidine-4,6-dicarboxylic acid bis(3-chloro-4-fluorobenzylamide) (formula I: R1 =
 Cl; R2 = F)



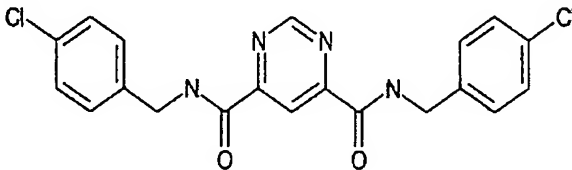
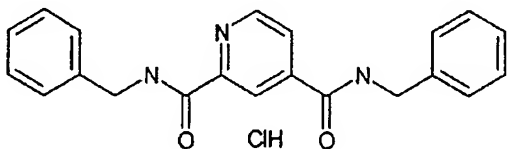
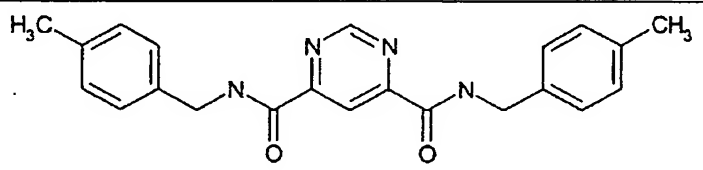
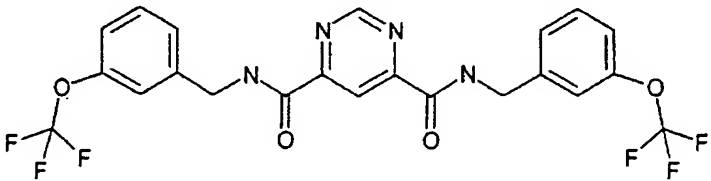
200 mg (1.2 mmol) of pyrimidine-4,6-dicarboxylic acid were suspended in 0.3 ml
 25 (4.1 mmol) of thionyl chloride. This mixture was heated at 85°C for 2 h while being
 stirred. After it had been cooled down to room temperature, 2 ml of absolute
 dichloromethane were added. The suspension was cooled down to 0°C and 0.33 ml
 (2.4 mmol) of triethylamine was added. 861 mg (5.4 mmol) of 3-chloro-4-
 fluorobenzylamine were added while stirring vigorously. The mixture was then stirred
 30 for a further 15 minutes. It was then diluted with 10 ml of dichloromethane after

which 10 ml of water were added. After 5 minutes, the mixture was transferred into a separating funnel and the phases were separated. The organic phase was extracted twice with saturated sodium chloride solution and then dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the residue which was obtained in this way was dissolved in ethyl acetate. The product was crystallized from the solution by adding heptane. Beige-colored flakes were obtained and were dried under reduced pressure.

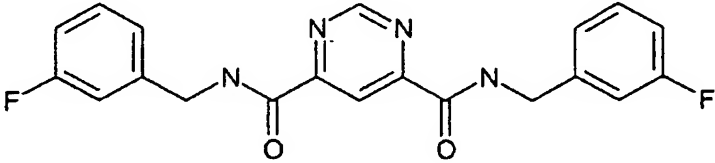
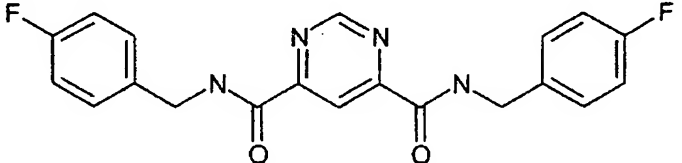
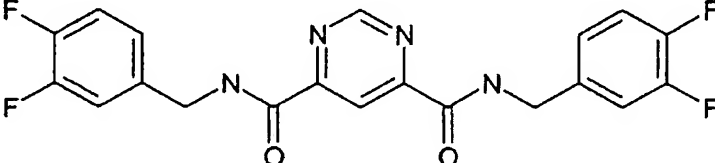
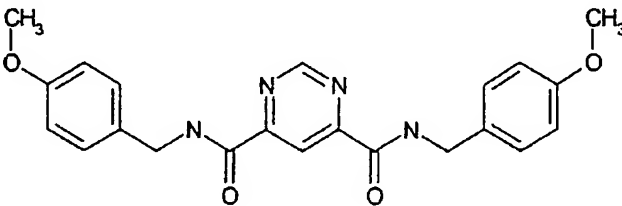
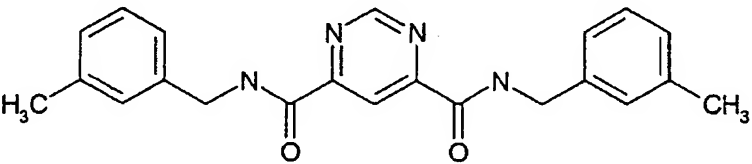
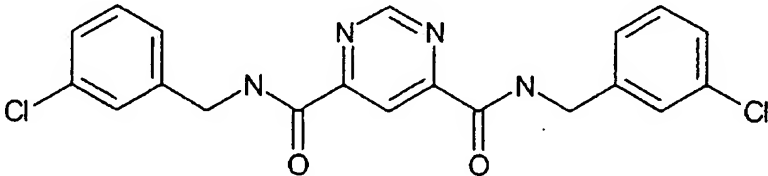
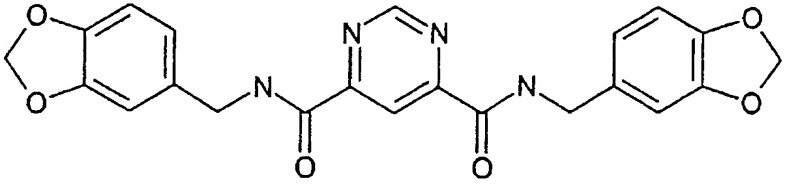
Yield: 263 mg (49%)

10 The following compounds were prepared in analogy with example 2.

Table 1:

Example	Structure	MS (ESI+)
3		415.13
4		346.27
5		375.26
6		515.21

7		382.21
8		374.25
9		406.31
10		419.22
11		483.24
12		414.15
13		560.18 (M+MeCN)

14		383.17
15		383.15
16		419.02
17		407.23
18		375.13
19		415.06
20		435.22

21		407.30
22		431.06
23		411.25

Example 24 Dimethyl pyrimidine-4,6-dicarboxylate

10 g (0.059 mol) of pyrimidine-4,6-dicarboxylic acid were suspended in 1.4 l of methanol, after which 10.93 ml (0.356 mol) of concentrated hydrochloric acid were added and the mixture was stirred under reflux (65°C) for 3 hours (h). The reaction mixture was concentrated under reduced pressure after which the residue was taken up once again in methanol; the mixture was filtered and the resulting solution was concentrated.

Yield 11.02 g (94.4%) MS (ES⁺): m/e = 197.20

2.55 g (0.01299 mol) of the resulting compound dimethyl pyrimidine-4,6-dicarboxylate were dissolved in 100 ml of dimethylformamide (DMF), after which 1.42 ml (0.01299 mol) of benzylamine were added and the mixture was heated to 50°C. After 4 h, the solution is concentrated under reduced pressure. The residue is chromatographed through a 500 ml silica gel column using heptane/ethyl acetate (1:1). Fractions containing the compound methyl 6-benzylcarbamoylpyrimidine-4-carboxylate were concentrated. Yield: 1.268 g (36%) MS (ES⁺): m/e = 272.20

200 mg (0.737 mmol) of the resulting compound methyl 6-benzylcarbamoylpyrimidine-4-carboxylate were dissolved in 4 ml of DMF, after which 225.98 mg (1.29

mmol) of 3-trifluoromethylbenzylamine were added and the mixture was stirred at 50°C for 1 day. After that, the solution was concentrated under reduced pressure. The residue was purified by means of preparative HPLC (water/acetonitrile gradient, Purospher RP18). Fractions containing pyrimidine-4,6-dicarboxylic acid 4-benzyl-
 5 amide-6-(3-trifluoromethylbenzylamide) were concentrated under reduced pressure and freeze-dried.

Yield: 240 mg (79%) MS (ES⁺): m/e = 415.27

The following compounds were prepared in an analogous manner:

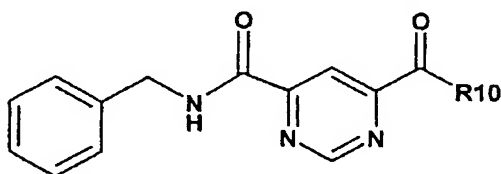


Table 2

Example	R10 radical	MS (ES ⁺): m/e
25	3-fluorobenzylamine	365.23
26	4-fluorobenzylamine	365.23
27	3,4-difluorobenzylamine	383.27
28	4-methoxybenzylamine	377.28
29	3-methylbenzylamine	361.28
30	3-chlorobenzylamine	381.23

Pharmacological examples

15 Determining the enzymic activity of the catalytic domain of human collagenase-3 (MMP-13).

This protein is obtained as an inactive proenzyme from INVITEK, Berlin (catalog No. 30 100 803). Activation of the proenzyme:

20 2 parts by volume of proenzyme are incubated with 1 part by volume of APMA solution at 37°C for 1.5 hours. The APMA solution is prepared from a 10 mmol/l solution of p-aminophenylmercuric acetate in 0.1 mmol/l NaOH by diluting it with 3 parts by volume of Tris/HCl buffer, pH 7.5 (see below). The pH is adjusted to

between 7.0 and 7.5 by adding 1 mmol/l HCl. After the enzyme has been activated, it is diluted with the Tris/HCl buffer down to a concentration of 1.67 $\mu\text{g/ml}$.

- In order to measure the enzyme activity, 10 μl of enzyme solution are incubated for
- 5 15 minutes with 10 μl of a buffered 3% (v/v) solution of dimethyl sulfoxide (reaction 1). In order to measure the enzyme inhibitor activity, 10 μl of enzyme solution are incubated with 10 μl of a buffered 3% (v/v) solution of dimethyl sulfoxide which contains the enzyme inhibitor (reaction 2).
- 10 Both in reaction 1 and in reaction 2, the enzyme reaction is monitored by fluorescence spectroscopy (328 nm (extinction)/393 nm (emission)) after 10 μl of a 3% (v/v) aqueous solution of dimethyl sulfoxide containing 0.75 mmol of the substrate/l have been added.
- 15 The enzyme activity is presented as increase in extinction/minute. The inhibitor effect is calculated as percentage inhibition in accordance with the following formula:
- $$\% \text{ inhibition} = 100 - [(\text{increase in extinction/minute in reaction 2}) / (\text{increase in extinction/minute in reaction 1}) \times 100].$$
- 20 The IC_{50} , i.e. the concentration of inhibitor which is required for a 50% inhibition of the enzyme activity, is determined graphically by plotting the percentage inhibitions at different inhibitor concentrations.

The buffer solution contains 0.05% Brij (Sigma, Deisenhofen, Germany) and also

25 0.1 mol of Tris/HCl/l, 0.1 mol of NaCl/l and 0.01 mol of CaCl_2/l (pH=7.5).

The enzyme solution contains 1.67 μg of the enzyme domain/ml.

The substrate solution contains 0.75 mmol of the fluorogenic substrate (7-methoxy-coumarin-4-yl)acetyl-Pro-Leu-Gly-Leu-3-(2'.4'-dinitrophenyl)-L-2,3-diaminopropionyl-

30 Ala-Arg-NH₂/l (Bachem, Heidelberg, Germany).

The following table 2 shows the results.

Table 3:

Example	IC50 MMP13 (nM)	Example	IC50 MMP13 (nM)
1	400	13	210
2	23	14	200
3	5600	15	190
4	3400	16	105
5	2000	17	80
6	700	18	72
7	620	19	57
8	400	20	14
9	320	21	10
10	300	22	9
11	300	23	8
12	260		

Comparative example

5

The compound pyrimidine-4,6-dicarboxylic acid diethylamide was prepared as described in EP 0418797. A value of 90 000 nM was obtained when the IC50 value for the inhibition of human collagenase -3 (MMP-13) was determined as described in the above example. This compound therefore has practically no inhibitory effect on

10

Determining the enzymic activity of the catalytic domains of human neutrophil collagenase (MMP-8) and human stromelysin (MMP-3).

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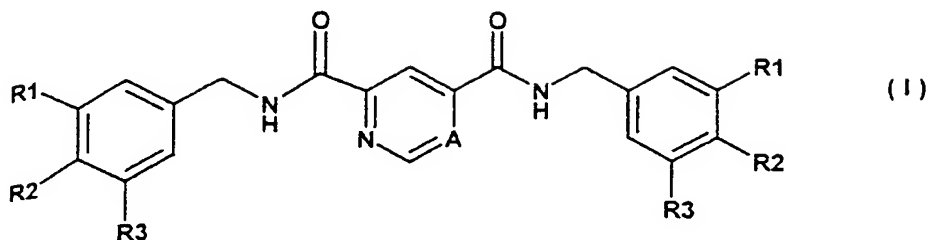
The enzymes human neutrophil collagenase and human stromelysin were prepared, carried out as active catalytic domains as described in Weithmann et al Inflamm Res, 46 (1997), pages 246-252. The measurement of the activity of the enzymes, and the determination of the inhibitory effect of inhibitors on the activity of the enzymes, were also carried out as described in that publication.

20

The compounds according to the abovementioned examples 1 to 23 in each case exhibited IC₅₀ values of more than 100 000 nM when determining human neutrophil collagenase and human stromelysin. These compounds therefore have practically no inhibitory effect on MMP 3 and MMP 8.

We claim:

1. A compound of the formula I,



and/or all the stereoisomeric forms of the compound of the formula I and/or mixtures of these forms in any ratio, and/or a physiologically tolerated salt of the compound of the formula I, wherein

A is a carbon atom or nitrogen atom,

R1 and R3 are identical or different and are, independently of each other,

1. hydrogen atom,
2. $-(C_1-C_4)$ -alkyl, in which alkyl is substituted once, twice or three times by halogen, or
3. $-O-(C_1-C_4)$ -alkyl, in which alkyl is substituted once, twice or three times by halogen,
4. $-OH$,
5. $-C(O)-O-R_4$, in which R_4 is hydrogen atom or $-(C_1-C_4)$ -alkyl,
6. $-CN$,
7. $-N(R_5)(R_6)$, in which R_5 and R_6 are identical or different and are, independently of each other,
 1. hydrogen atom,
 2. $-(C_1-C_4)$ -alkyl,
 3. $-C(O)-(C_1-C_4)$ -alkyl or
 4. $-SO_2-(C_1-C_4)$ -alkyl,
8. $-S-(C_1-C_4)$ -alkyl,
9. $-S(O)-(C_1-C_4)$ -alkyl, or
10. $-S(O)_2-R_7$, in which R_7 is $-(C_1-C_4)$ -alkyl, $-OH$ or $-NH_2$,

in which R1, R2 and R3 are not simultaneously hydrogen atom, and

R2 is 1. hydrogen atom,

2. halogen,
 3. -O-(C₁-C₄)-alkyl,
 4. -(C₁-C₄)-alkyl,
 5. -C(O)-O-R₄, in which R₄ is hydrogen atom or -(C₁-C₄)-alkyl,
 - 5 6. -CN,
 7. -N(R₅)(R₆), in which R₅ and R₆ are identical or different and are,
independently of each other,
 1. hydrogen atom,
 2. -(C₁-C₄)-alkyl,
 - 10 3. -C(O)-(C₁-C₄)-alkyl, or
 4. -SO₂-(C₁-C₄)-alkyl,
 8. -OH,
 9. -S-(C₁-C₄)-alkyl,
 10. -S(O)-(C₁-C₄)-alkyl, or
 - 15 11. -S(O)₂-R₇, in which R₇ is -(C₁-C₄)-alkyl, -OH or -NH₂, or
- R₁ and R₂ or R₂ and R₃ form, together with the carbon atoms to which they are in each case bonded, a 5- or 6-membered ring which is aromatic or saturated and contains zero, one or two heteroatoms from the series oxygen, nitrogen or sulfur, and
- 20 the other radical R₁ or R₃ is
1. hydrogen atom,
 2. halogen,
 3. -(C₁-C₄)-alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
 - 25 4. -O-(C₁-C₄)-alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
 5. -C(O)-O-R₄, in which R₄ is hydrogen atom or -(C₁-C₄)-alkyl,
 6. -CN,
 7. -N(R₅)(R₆), in which R₅ and R₆ are identical or different and are,
independently of each other,
 1. hydrogen atom,
 2. -(C₁-C₄)-alkyl,
- 30

3. $-\text{C}(\text{O})-(\text{C}_1-\text{C}_4)\text{-alkyl}$ or
4. $-\text{SO}_2-(\text{C}_1-\text{C}_4)\text{-alkyl}$,
8. $-\text{OH}$,
9. $-\text{S}-(\text{C}_1-\text{C}_4)\text{-alkyl}$,
- 5 10. $-\text{S}(\text{O})-(\text{C}_1-\text{C}_4)\text{-alkyl}$ or
11. $-\text{S}(\text{O})_2\text{-R}_7$, in which R_7 is $-(\text{C}_1-\text{C}_4)\text{-alkyl}$, $-\text{OH}$ or $-\text{NH}_2$.

2. A compound of the formula I as claimed in claim 1, wherein

A is a carbon atom or nitrogen atom,

10

R_1 and R_3 are identical or different and are, independently of each other,

1. hydrogen atom,
2. chlorine,
3. fluorine,
- 15 4. trifluoromethyl,
5. methoxyl,
6. methyl,
7. $-\text{C}(\text{O})-\text{OH}$,
8. $-\text{C}(\text{O})-\text{O}-\text{CH}_3$,
- 20 9. $-\text{CN}$,
10. $-\text{NH}_2$,
11. $-\text{NH}-\text{C}(\text{O})-\text{CH}_3$,
12. $-\text{NH}-\text{SO}_2-\text{CH}_3$,
13. $-\text{N}(\text{CH}_3)_2$,
- 25 14. $-\text{SO}_2-\text{NH}_2$,
15. $-\text{OH}$,
16. $-\text{O}-\text{CH}_2-(\text{CHF}_2)$,
17. $-\text{S}-\text{CH}_3$,
18. $-\text{S}(\text{O})-\text{CH}_3$,
- 30 19. $-\text{S}(\text{O})_2-\text{CH}_3$ or
20. bromine,

in which R_1 , R_2 and R_3 are not simultaneously hydrogen atom, and

R2 is 1. hydrogen atom,

2. chlorine,

3. fluorine,

4. methoxyl,

5 5. methyl,

6. bromine,

7. -C(O)-OH,

8. -C(O)-O-CH₃,

9. -CN,

10 10. -NH₂,

11. -NH-C(O)-CH₃,

12. -NH-SO₂-CH₃,

13. -N-(CH₃)₂,

14. -SO₂-NH₂,

15 15. -OH,

16. -O-CH₂-(CHF₂),

17. -S-CH₃,

18. -S(O)-CH₃ or

19. -S(O)₂-CH₃, or

20 R1 and R2 or R2 and R3 form, together with the carbon atoms to which they are in each case bonded, a dioxolane, dihydrofuran or furan ring and the other radical R1 or R3 has the abovementioned meaning of 1. to 20.

3. A compound of the formula I as claimed in claim 1 or 2, and/or all the
25 stereoisomeric forms of the compound of the formula I and/or mixtures of these forms in any ratio, and/or a physiologically tolerated salt of the compound of the formula I, wherein

A is a carbon atom or nitrogen atom,

30 R1 and R3 are identical or different and are, independently of each other,

1. hydrogen atom,

2. -(C₁-C₄)-alkyl, in which alkyl is substituted once, twice or three times by halogen, or

3. -O-(C₁-C₄)-alkyl, in which alkyl is substituted once, twice or three times by halogen,

in which R₁, R₂ and R₃ are not simultaneously hydrogen atom, and

R₂ is 1. hydrogen atom,

2. halogen,

3. -O-(C₁-C₄)-alkyl, or

4. -(C₁-C₄)-alkyl, or

R₁ and R₂ or R₂ and R₃ form, together with the carbon atoms to which they are in each case bonded, a 5- or 6-membered ring which is aromatic or saturated and contains zero, one or two heteroatoms from the series oxygen, nitrogen or sulfur, and

the other radical R₁ or R₃ is

1. hydrogen atom,

2. halogen,

3. -(C₁-C₄)-alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen, or

4. -O-(C₁-C₄)-alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen.

4. A compound of the formula I as claimed in one or more of claims 1 to 3, wherein

A is a carbon atom or nitrogen atom,

R₁ and R₃ are identical or different and are, independently of each other,

1. hydrogen atom, or

2. trifluoromethyl,

in which R₁, R₂ and R₃ are, not simultaneously, hydrogen atom, and

R₂ is 1. hydrogen atom,

2. chlorine,

3. fluorine,

4. methoxyl or

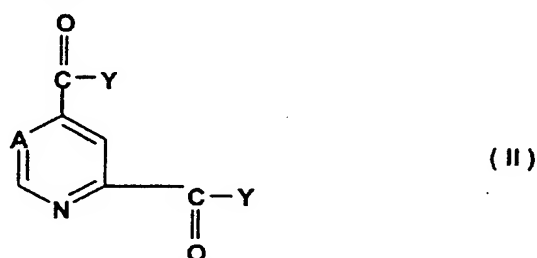
5. methyl, or

R₁ and R₂ or R₂ and R₃ form, together with the carbon atoms to which they are in each case bonded, a dioxolane, dihydrofuran or furan ring, and

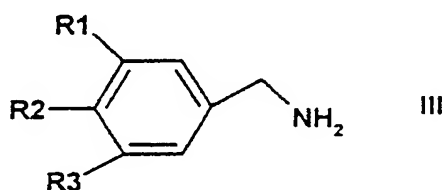
the other radical R1 or R3 is

1. hydrogen atom,
2. chlorine,
3. fluorine,
4. trifluoromethyl,
5. methoxyl, or
4. methyl.

5. A process for preparing the compound of the formula I as claimed in one or more of Claims 1 to 4, which comprises reacting a compound of the formula II

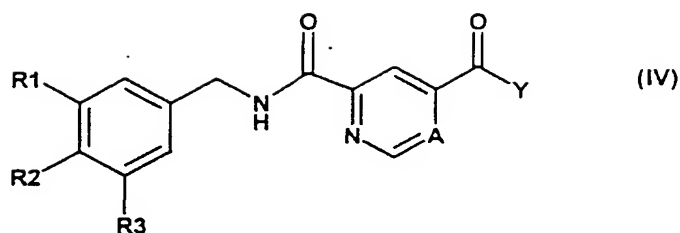


- a) with a compound of the formula III



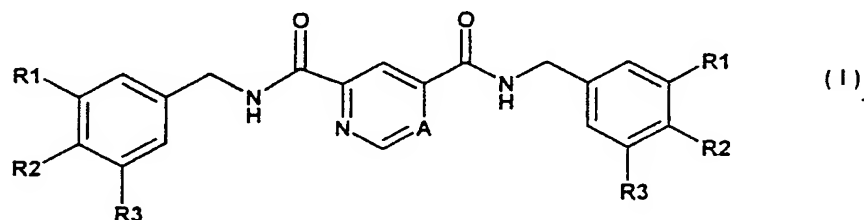
where R1, R2 and R3 have the meanings given in formula I as claimed in claim 1, and Y is halogen, hydroxy or C₁-C₄-alkoxy or, together with the carbonyl group, forms an active ester or a mixed anhydride, with a compound of the formula I being formed and the reaction products being converted, where appropriate, into their physiologically tolerated salts, or

- b) reacting a compound of the formula II with a compound of the formula III to give a compound of the formula IV



where R1, R2 and R3 have the meanings given in formula I as claimed in claim 1, and Y is halogen, hydroxy or C₁-C₄-alkoxy or, together with the carbonyl group, forms an active ester or a mixed anhydride, and then purifying the resulting compound of the formula IV, where appropriate, and then converting it, with a compound of the formula III, into a compound of the formula I.

6. A pharmaceutical which comprises an effective content of at least one compound of the formula I as claimed in one or more of claims 1 to 4 together with a pharmaceutically suitable and physiologically tolerated carrier substance, additive and/or other active compounds and auxiliary substances.
7. The use of the compound of the formula I



and/or all the stereoisomeric forms of the compound of the formula I and/or mixtures of these forms in any ratio, and/or a physiologically tolerated salt of the compound of the formula I

for producing a pharmaceutical for the prophylaxis and therapy of diseases whose course involves an increased activity of matrix metalloproteinase 13, wherein

A is a carbon atom or nitrogen atom,

R1 and R3 are identical or different and are, independently of each other,

1. hydrogen atom,
2. halogen,
3. $-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
- 5 4. $-O-(C_1-C_4)$ -alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
5. $-C(O)-O-R_4$, in which R_4 is hydrogen atom or $-(C_1-C_4)$ -alkyl,
6. $-CN$,
7. $-N(R_5)(R_6)$, in which R_5 and R_6 are identical or different and are,
10 independently of each other,
 1. hydrogen atom,
 2. $-(C_1-C_4)$ -alkyl,
 3. $-C(O)-(C_1-C_4)$ -alkyl or
 4. $-SO_2-(C_1-C_4)$ -alkyl,
- 15 8. $-OH$,
9. $-S-(C_1-C_4)$ -alkyl,
10. $-S(O)-(C_1-C_4)$ -alkyl,
11. $-S(O)_2-R_7$, in which R_7 is $-(C_1-C_4)$ -alkyl, $-OH$ or $-NH_2$,
- 20 R2 is 1. hydrogen atom,
2. halogen,
3. $-O-(C_1-C_4)$ -alkyl,
4. $-(C_1-C_4)$ -alkyl,
5. $-C(O)-O-R_4$, in which R_4 is hydrogen atom or $-(C_1-C_4)$ -alkyl,
- 25 6. $-CN$,
7. $-N(R_5)(R_6)$, in which R_5 and R_6 are identical or different and are,
independently of each other,
 1. hydrogen atom,
 2. $-(C_1-C_4)$ -alkyl,
 - 30 3. $-C(O)-(C_1-C_4)$ -alkyl or
 4. $-SO_2-(C_1-C_4)$ -alkyl,
 8. $-OH$,

9. -S-(C₁-C₄)-alkyl,
10. -S(O)-(C₁-C₄)-alkyl,
11. -S(O)₂-R₇, in which R₇ is -(C₁-C₄)-alkyl, -OH or -NH₂, or

R₁ and R₂ or R₂ and R₃ form, together with the carbon atoms to which they are in each case bonded, a 5- or 6-membered ring which is aromatic or saturated and contains zero, one or two heteroatoms from the series oxygen, nitrogen or sulfur, and the other radical R₁ or R₃ has the abovementioned meaning of 1. to 11.

8. The use as claimed in claim 7, which comprises employing a compound of the formula I wherein

A is a carbon atom or nitrogen atom,

R₁ and R₃ are identical or different and are, independently of each other,

1. hydrogen atom,
2. halogen,
3. -(C₁-C₄)-alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,
4. -O-(C₁-C₄)-alkyl, in which alkyl is unsubstituted or substituted once, twice or three times by halogen,

- R₂ is
1. hydrogen atom,
 2. halogen,
 3. -O-(C₁-C₄)-alkyl, or
 4. -(C₁-C₄)-alkyl, or

R₁ and R₂ or R₂ and R₃ form, together with the carbon atoms to which they are in each case bonded, a 5- or 6-membered ring which is aromatic or saturated and contains zero, one or two heteroatoms from the series oxygen, nitrogen or sulfur, and

the other radical R₁ or R₃ has the abovementioned meaning of 1. to 4.

9. The use as claimed in claims 7 and 8, which comprises employing a compound for the formula I wherein

A is a carbon atom or nitrogen atom,

5 R1 and R3 are identical or different and are, independently of each other,

1. hydrogen atom,
2. chlorine,
3. fluorine,
4. trifluoromethyl,

10 5. methoxyl,

6. methyl,

7. -C(O)-OH,

8. -C(O)-O-CH₃,

9. -CN,

15 10. -NH₂,

11. -NH-C(O)-CH₃,

12. -NH-SO₂-CH₃,

13. -N-(CH₃)₂,

14. -SO₂-NH₂,

20 15. -OH,

16. -O-CH₂-(CHF₂),

17. -S-CH₃,

18. -S(O)-CH₃,

19. -S(O)₂-CH₃ or

25 20. bromine,

R2 is 1. hydrogen atom,

2. chlorine,

3. fluorine,

30 4. methoxyl,

5. methyl,

6. bromine,

7. -C(O)-OH,

8. $-\text{C}(\text{O})-\text{O}-\text{CH}_3$,
9. $-\text{CN}$,
10. $-\text{NH}_2$,
11. $-\text{NH}-\text{C}(\text{O})-\text{CH}_3$,
12. $-\text{NH}-\text{SO}_2-\text{CH}_3$,
13. $-\text{N}-(\text{CH}_3)_2$,
14. $-\text{SO}_2-\text{NH}_2$,
15. $-\text{OH}$,
16. $-\text{O}-\text{CH}_2-(\text{CHF}_2)$,
17. $-\text{S}-\text{CH}_3$,
18. $-\text{S}(\text{O})-\text{CH}_3$ or
19. $-\text{S}(\text{O})_2-\text{CH}_3$, or

R1 and R2 or R2 and R3 form, together with the carbon atoms to which they are in each case bonded, a dioxolane, dihydrofuran or furan ring, and the other radical R1 or R3 has the abovementioned meaning of 1. to 20.

10. The use as claimed in one or more of claims 7 to 9 which comprises employing a compound of the formula I wherein

A is a carbon atom or nitrogen atom,

R1 and R3 are identical or different and are, independently of each other,

1. hydrogen atom,
2. chlorine,
3. fluorine,
4. trifluoromethyl,
5. methoxyl, or
6. methyl,

R2 is

1. hydrogen atom,
2. chlorine,
3. fluorine,
4. methoxyl, or
5. methyl, or

R1 and R2 or R2 and R3 form, together with the carbon atoms to which they are in each case bonded, a dioxolane, dihydrofuran or furan ring.

11. The use as claimed in one or more of claims 7 to 10, wherein the diseases
5 whose course involves an increased activity of matrix metalloproteinase 13
are the degenerative joint diseases such as osteoarthroses, osteoarthritis,
spondyloses, chondrolysis following joint trauma or a relatively long period of
joint immobilization following injuries to the meniscus or patella or tearing of a
ligament, diseases of the connective tissue such as collagenoses, periodontal
10 diseases and wound healing disturbances, chronic diseases of the locomotor
system, such as inflammatory, immunologically or metabolism-determined
acute and chronic arthritides, arthropathies, myalgias and disturbances of
bone metabolism.

Abstract

5

Use of pyridine-2,4-dicarboxylic acid diamides and pyrimidine-4,6-dicarboxylic acid diamides for selectively inhibiting collagenases

10

Pyridine-2,4-dicarboxylic acid diamides and pyrimidine-4,6-dicarboxylic acid diamides for selectively inhibiting collagenase (MMP 13). The pyridine-2,4-dicarboxylic acid diamides and pyrimidine-4,6-dicarboxylic acid diamides can therefore be used for treating degenerative joint diseases.